Missouri
Botanical
Garden

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Ladies and Gentlemen:

I wish to comment regarding your draft guidelines, Docket No. OOD-1392, on Botanical Drug Products. I am a plant systematist presently working on a manual to assist in the identification of important herbal supplement species. The comments below represent a synthesis of my opinions and those of my immediate superior, Dr. James Miller, the head of the Applied Research Department at the Missouri Botanical Garden. We see potential criticisms of the guidelines in the areas of nomenclature, authentication of raw materials, and requirements for uniformity of source material and drug product.

Manufacturers are instructed to provide "[n]ame of variety, species, genus, and family, including the name of the botanist who first described the species or variety, if known." We feel that a Latin binomial with authority should be required at all times: the authority's name is part of a plant's scientific name, and the incidence of homonyms (identical names accidentally created by different botanists) is high. For example, *Matricaria chamomilla* L. is one name used for German chamomile, whereas *Matricaria chamomilla* Blanco was applied to a species of chrysanthemum. Family name is often a matter of opinion – there are at least three different "correct" family names for *Aloe vera*, depending upon whose classification of the monocots you accept – and is unnecessary, as the binomial with authority unambiguously identifies the plant.

At certain points, "proper identification by trained personnel" is required. It should be recognized that proper identification of unfamiliar plants often requires not only basic botanical knowledge but access to material of known identity. Even a professional botanist may err in identifying an unknown plant from books, and if no herbarium sheet is available for purposes of comparison, he may have no way of knowing that he has erred. The acquisition of reference standards can address this problem, but the guidelines do not mention reference standards until Phase 3. Incidentally, it seems strange that proper identification is not required in Phases 1 or 2 for lawfully marketed botanicals. The prior use of an herb does not mean that it is automatically recognizable, and substitutions at this stage might result in spurious negative results that prevented Phase 3 trials from taking place.

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"A certificate of authenticity signed by a trained botanist" is suggested or required as well. FDA should be more specific here about what is requested. "Trained botanist" is of uncertain meaning – we do not feel that any particular academic degree is absolutely required to qualify as a botanist, for example. Can the botanist be on the company's payroll, as is the employee who does the "proper identification"? If he is not an employee of the company that produced the raw material, potential conflict of interest is reduced. Unless he is already experienced with the species in question, he should have access to authenticated reference material or herbarium collections. Finally, in Phases 1 and 2 the provision of such a certificate, if available, is requested for legally marketed botanicals that are sold only outside the United States. The sale of a product in the U.S. is no guarantee that authenticity is not an issue (for example: ginseng products with no detectable ginseng), thus FDA should encourage manufacturers to provide certificates for every botanical, as they will have to do anyway in Phase 3.

FDA should also make sure that the distinction between vouchers and reference material is clear to industry, and possibly suggest proper procedures for the selection and storage of voucher material. FDA confuses the former issue in Phase 3 by asking for a "voucher specimen...retained for every batch" and for a "specimen of the botanical raw material retained as the reference standard." This will encourage companies to set aside one piece as a "reference" and the next as a "voucher." The company must by necessity produce its own reference standard for processed material. However, the reference material kept for raw botanicals preferably should not come out of the same crate as the material that is to be processed. It should come from an independent source if possible, so that identity of voucher material can be confirmed by direct comparison. If previously authenticated reference material cannot be obtained from another source, selected material should always be sent to an independent expert for confirmation of identity before it can be considered a reference standard.

By contrast, vouchers from each lot are preserved for examination in case there are future questions about the identity of raw materials. If material is obtained in an intact state or in large pieces, vouchers should of course be preserved at that time. We also keep "grinding vouchers" from plant samples that are processed through grinding or powdering; this would, among other things, allow the powdered voucher material to be compared with a powdered reference standard. If both grinding vouchers and whole vouchers are kept from a batch, they should share a single number so that they may easily be associated. It might be desirable for some excess voucher material to be placed in herbaria or economic botany collections, to allow some access to outside researchers; however, we recognize a company's legitimate need to maintain control over specimens that may serve as legal protection. In any case, consideration should always be given to the means of storing voucher material so as to preserve its usefulness for a period of years.

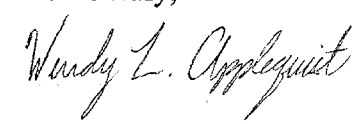
We think that FDA's insistence on both identical sources and identical finished product from batch to batch is not compatible with biological reality, and is likely to be an unattainable standard. The Phase 3 requirements state that each batch of the drug must be identical in a battery of chemical tests. Even if the quantities of all suspected active compounds were identical, a drug would fail if some unimportant metabolites were present to varying degrees. It is the nature of plants, as very complex living organisms, to vary in response to their environment. Even if all plants ever harvested were genetically identical, those harvested in a wet year would not be biochemically identical to those harvested in a dry year. FDA's demand that "[a]ll chemical constituents present...should be qualitatively and quantitatively comparable," even if they are not pharmacologically important, could make it virtually impossible to produce botanical drugs if sensitive tests were applied. To make some characteristic of a botanical product repeatable – for example, making a cup of tea taste the same from one lot to the next – manufacturers may go to great effort to blend slightly different raw materials in varying proportions as needed. FDA has, in our opinion unwisely, prohibited this option by specifying that "[i]f more than one variety or source of a given species is used, they should be blended in a fixed proportion in a consistent manner."

We also have concerns about the definition of "variety or source." "Variety" has a defined taxonomic meaning as a formally recognized infraspecific unit, and it is appropriate to specify what varieties are included in a drug, as varieties may differ biochemically. "Source" is completely undefined: does this mean a chemovar or cultivar, or does it mean that if the manufacturer has used the material of only one grower during trials, only that grower's material can legally be put into the drug product? Moreover, some crops, for example, tropical woods and barks, are not amenable to large-scale farming of identical plants. How are manufacturers to deal with wildcrafted material: is a "source" a single supplier purchasing from some group of harvesters? Would switching to a supplier of higher-quality material mean starting over from scratch? Even if multiple suppliers are lined up, the "fixed proportion" requirement ignores the difficulties of obtaining material reliably from some parts of the world (and if one of the suppliers goes out of business, there goes the fixed proportion). Or can a "source" be a geographical area, and if so, how large? If FDA proposes that all finished product must be chemically identical, it certainly does not matter if raw material comes from more than one place; if the product is functionally identical, it also is unlikely to matter.

It also appears that, after reading these guidelines, manufacturers will feel significant pressure to come up with molecular explanations of drug action. There are repeated requests for tests involving active constituents, and "[i]f the identity of the active constituents is not known or a suitable assay cannot be developed, the characteristic markers should be demonstrated to be clinically relevant...." If all batches share a similar chemical profile and the drug's effectiveness is

demonstrated, this requirement seems redundant, although easily met so long as a dose-response effect exists. Finally, "[i]nteractions with other commonly used medicines...should be investigated extensively. This may include characterization of the metabolic enzymes and/or pathway affected by the drug." This is a potentially limitless task, and the interactions of single compounds with other single compounds or with botanicals are often identified only by the adverse reaction reporting system; we can hardly demand more of botanicals. There are many single compounds on the market whose molecular effects are not well understood in general. Botanicals, containing multiple compounds that may act synergistically, are many times more complicated; there are botanicals such as *Hypericum* for which biological effects have been clearly demonstrated, yet serious dispute continues regarding the identity of the active compounds, to say nothing of the means of their activity. If American consumers are to benefit from botanical drugs, FDA should focus on confirming that they are safe and effective. Given the limited money, years, personnel, and lab facilities that a company can invest in any botanical, we must accept that it will often be unfeasible to define its action at the molecular level.

Yours truly,



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